passively administered tetanus immune globulin.

4. *Critique.* In view of the product's ability to meet the minimum requirements including the potency test in animals, it is adequate for booster use in humans. However, no data are available to demonstrate its efficacy as a primary immunizing agent.

Two matters are of fundamental concern: (a) The Lf content of this product may be excessively high, inviting excessive reactions or possibly even suggesting poor antigenic quality; (b) in the opinion of some, there is no need for a fluid product in view of the superiority of adsorbed products.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy and rate of adverse reactions of this product when used for primary immunization. Labeling revisions are required.

Tetanus Toxoid, Fluid, Manufactured by Wyeth Laboratories, Inc.

1. *Description.* This is a fluid preparation of tetanus toxoid containing 5 Lf of tetanus toxoid per 0.5 mL with 1:10,000 thimerosal as a preservative. Sodium chloride is the diluent.

2. *Labeling*—a. *Recommended use/indications.* This preparation is recommended for active immunization against tetanus but is is specified that the adsorbed preparation is preferred both for basic immunization and recall doses. Otherwise the recommended use/indications are identical to those of the Public Health Service Advisory Committee on Immunization Practices and the Committee on Infectious Diseases of the American Academy of Pediatrics. For primary immunization, 3 doses at 4-week intervals followed by a reinforcing dose 6 to 12 months later, all at 0.5 mL, are recommended. Routine reinforcing doses at 10-year intervals are recommended, and recommendations for reinforcing doses with injury follow those of public advisory groups. The package insert describes techniques for administration in detail. Fractional doses are recommended for children with cerebral damage, neurological disorders, or a history of febrile convulsions. Included are warnings about the transmission of serum hepatitis as a result of improper techniques, the possibility of inadequate immunization of individuals receiving immuno-suppresive drugs, the need to determine whether there was an untoward reaction to a prior dose, and the possibility of rare allergic reactions.

b. *Contraindications.* An acute respiratory or other infection is specified as a contraindication to routine immunization, but is not included as a contraindication to a recall dose following injury. No other specific contraindication is listed.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data regarding the efficacy of this specific product in humans are provided.

b. *Safety*—(1) *Animal.* Although no data were provided with the submission, the product meets Federal requirements.

(2) *Human.* No data regarding safety in humans are provided.

c. *Benefit/risk ratio.* Presumably this product has a satisfactory benefit-to-risk assessment for primary immunization although specific data with which to determine this with precision are not available. The benefit-to-risk assessment is satisfactory for booster immunization.

4. *Critique.* It is likely that this product is efficacious and quite safe, although specific data are not available. The Panel does have some doubts about the need for fluid tetanus toxoid preparations in the light of the apparent superiority of adsorbed products.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Tetanus Toxoid Adsorbed Manufactured by Wyeth Laboratories, Inc.

1. *Description.* This is an aluminum phosphate adsorbed tetanus toxoid containing 5 Lf of tetanus toxoid per 0.5 mL. It is preserved in 1:10,000 thimerosal and diluted in saline.

2. *Labeling*—a. *Recommended use/indications.* For primary immunization, 2 injections of 0.5 mL at 4-week intervals followed by a reinforcing dose 6 to 12 months later are recommended. Routine reinforcing doses are recommended at 10 year intervals. The current recommendations of the Public Health Service Advisory Committee on Immunization Practices and the Committee on Infectious Disease of the American Academy of Pediatrics are included. However, it is not stated to what populations this specific preparation should be administered. There is no mention of the preferability of combined preparations containing diphtheria toxoids and pertussis vaccine for routine administration.

Techniques for administration are very well described. Fractional doses are recommended for children with cerebral damage, neurological disorders, or history of febrile convulsions. Warning about the transmission of serum hepatitis with improper techniques, the possibility of inadequate immunization of individuals on immunosuppressive drugs, the need to determine whether there was an undue reaction to a prior injection, and rare allergic reactions are included.

b. *Contraindications.* An acute respiratory or other infection is specified as a contraindication except when the reinforcing dose is required following injury. No other absolute contraindication is included.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* A review of the general efficacy of tetanus toxoid, adsorbed, is provided (Ref. 17), but there is no information relating to this specific product.

b. *Safety*—(1) *Animal.* Although no data were provided with the submission, this product meets Federal requirements.

(2) *Human.* The excellent safety record of tetanus toxoid in general is provided in the manufacturer's submission, but information relative to this specific product is not included.

c. *Benefit/risk ratio.* Although this product has been in use for many years and there is no reason to believe that the benefit-to-risk assessment is not satisfactory for primary immunizataion, no specific data are available. The benefit-to-risk assessment for booster immunization is satisfactory.

4. *Critique.* From the description of the methods employed in preparing this product and from the statement that

required animal testing for efficacy is undertaken, it would seem that this product is both safe and efficacious for booster immunization. However, specific data regarding safety in animals and both safety and efficacy in humans are not provided. The package insert does not specify populations to which this specific product should be given, and preference for combined preparations containing diphtheria toxoid and pertussis vaccine is not expressed.

5. *Recommendations.* The Panel recommends that his product be placed in Category I as regards its use for booster immunization and the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

References

(1) BER Volume 2072.
(2) BER Volume 2064.
(3) BER Volume 2026.
(4) Snyder, H.E., G. Edsall, and L. Levine, "Tetanus Immunization," *The Journal of Trauma,* 6:529–538, 1966.
(5) BER Volume 2114.
(6) BER Volume 2113.
(7) BER Volume 2032.
(8) BER Volume 2031.
(9) BER Volume 2056.
(10) BER Volume 2057.
(11) BER Volume 2011.
(12) BER Volume 2078.
(13) MacLennan, R., F. Goldfield, M. Pittman, M.C. Hardegree, et al., "Immunization Against Neonatal Tetanus in New Guinea. II. Antitoxin Response of Pregnant Women to Adjuvant and Plain Toxoids," *Bulletin of the World Health Organization,* 32:683–698, 1965.
(14) Hardegree, C., M. Barile, M. Pittman, et al., "Immunization Against Neonatal Tetanus in New Guinea," *Bulletin of the World Health Organization,* 43:439–451, 1970.
(15) BER Volume 2038.
(16) BER Volume 2103.
(17) BER Volume 2019.

Generic Statement

Diphtheria and Tetanus Toxoids (DT) for Pediatric Use

See Generic Statements for monovalent diphtheria and tetanus toxoids.

Description

The combination of diphtheria and tetanus toxoids for pediatric use (DT) is intended for the immunization of children against diphtheria and tetanus under circumstances in which the use of these two toxoids combined with pertussis vaccine is undesirable or contraindicated. Current licensed products include both fluid and adsorbed forms of DT.

Production

The manufacturing process basically comprises the production, detoxification, purification, and titration of the two toxoids independently. By Federal regulation, the individual toxoids for the adsorbed forms must be adsorbed prior to combination. Both the tetanus and diphtheria toxoids components must be tested for detoxification prior to combination. After combination, both components must be tested for antigenic potency in animals. Currently, there is striking variation among the licensed products in terms of the flocculation titers (Lf) for diphtheria and tetanus toxoids per dose. The ranges of Lf for diphtheria toxoids for the fluid product are 25 to 125 and 7.5 to 25 for the adsorbed product. The Lf range of tetanus toxoid is 5 to 10 for the adsorbed product and 5 to 40 for the fluid product.

Use and Contraindications

This product should be used for primary immunization and for booster doses for children 6 years of age or less in instances in which pertussis immunization is contraindicated. Thus, its major use would be for completion of immunization and for booster doses for children who have responded to the triple combination of diphtheria and tetanus toxoids and pertussis vaccine (DTP) with a significant reaction believed or suspected to be a consequence of the pertussis component. Under such circumstances completion of the primary immunization schedule with adsorbed DT is preferred and should comprise a series of 3 doses (considering the doses of DTP already given as part of the series) with the first 2 given 4 to 8 weeks apart and the third 1 year later. A booster dose of TD should be given at school entry, and subsequent booster doses should be given approximately every 10 years, employing tetanus and diphtheria toxoids combined for adult use (Td). Recommendations for immunization with fluid DT are identical except that the primary series should comprise 4 doses, with the first 3 being given 4 to 8 weeks apart and the fourth a year later. Circumstances may occur, such as outbreaks of diphtheria, in which it would be advantageous for individuals older than 6 years of age to receive a larger amount of diphtheria toxoid than is present in the Td (adult type). Diphtheria and tetanus toxoid may be considered for use under these circumstances.

The only contraindication to the administration of DT is a prior severe hypersensitivity reaction. It is also not recommended for use in individuals 7 years of age or older. It is advisable not to administer the product during a febrile illness because of possible confusion as to the cause of persistent fever if such should occur. Individuals receiving corticosteroids or other immunosuppressive drugs may not display an optimum immunologic response; accordingly, if discontinuation of such drugs is anticipated within the immediate future, immunization should be delayed until that time.

Safety

Both components of this combined product are tested for safety in animals and for sterility according to Federal requirements as with the monovalent toxoids.

Efficacy

Minimum requirements specify that the diphtheria toxoid component of the combined product may be tested for potency in guinea pigs either before or after combination, and that the tetanus toxoid component be tested for potency after combination. The Bureau of Biologics releases this combined product based on potency data as determined after combination. Neither the diphtheria nor the tetanus component exerts a significant adjuvant or suppressant effect upon the immunogenicity of the other.

Labeling

The labeling for some of the products is slightly inconsistent with the current recommendations of the Public Health Service Advisory Committee on Immunization Practices and the American Academy of Pediatrics in that these groups recommend that Td (for adult use) be used for children over 6 years of age. Accordingly, the labeling should be modified for DT (for pediatric use) to recommend that these products be used for children "six years of age and under," rather than for children "under six" as is the case with some of the labeling.

Special Problems

The same problems that exist in terms of the immunogenicity of these toxoids in the monovalent form exist in the combined form.

Recommendations

The recommendations made for the individual toxoid components apply to the combined product. It is also recommended that requirements be updated to stipulate testing for potency after combination of the individual products.

Basis for Classification

The basis for classification of this combined product is the same as the basis for classification of the individual toxoid components.

References

(1) Public Health Service Advisory Committee on Immunization Practices, "Diphtheria and Tetanus Toxoids and Pertussis Vaccine," *Morbidity and Mortality Weekly Report*, Suppl. 21(25):4–5, 1972.

(2) "Diphtheria—Tetanus—Pertussis," *in* "Center for Disease trol, United States Immunization Survey: 1975," Health, Education, and Welfare Publication No. (Center for Disease Control), 76–8221:25–30, 1977.

(3) Center for Disease Control, "Reported Morbidity and Mortality in the United States 1976," *Morbidity and Mortality Weekly Report*, Suppl. August 1977, Health, Education, and Welfare Publication No. (Center for Disease Control), 77–8241.

SPECIFIC PRODUCT REVIEWS

Diphtheria and Tetanus Toxoids Adsorbed Manufactured by Bureau of Laboratories, Michigan Department of Public Health

1. *Description.* This is a combined preparation containing 10 to 20 Lf of diphtheria toxoid and 5 to 10 Lf of tetanus toxiod per 0.5 mL. The toxoids are adsorbed on aluminum phosphate and preserved with 0.01 percent thimerosal.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for the active immunization of children less than 6 years of age. The recommended dosage comprises two 0.5 mL intramuscular injections 4 to 6 weeks apart followed by a reinforcing dose 6 to 12 months later. A further reinforcing dose of 0.5 mL is advised at 5 years of age. The preferability of primary immunization with a trivalent preparation containing pertussis vaccine is not mentioned. If a dose has not been administered within the previous year, the manufacturer recommends a reinforcing dose of this preparation under any one of five circumstances: Exposure to diphtheria; injury with risk of contracting tetanus; unusual prevalence or risk of exposure to diphtheria; change of environment; and disasters which result in crowding or dislocation.

b. ***Contraindications.*** It is recommended that tetanus and diphtheria toxoids, adsorbed, for adult use, be used to produce and maintain active immunity against tetanus and diphtheria in individuals 6 or more years of age because of reactivity of this product. A warning that previously unimmunized individuals will not be protected by this product in case of exposure to diphtheria or tetanus is included. It is also stated that this preparation is useless in the treatment of diphtheria or tetanus. Any acute respiratory disease or other active infection is considered a contraindication. Deferral of immunization is recommended in individuals receiving short-term immunosuppressive therapy and, in instances of long-term immunosuppressive therapy, an extra dose is recommended 1 or more months after therapy is discontinued.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The only data available concerning primary immunization of humans related to this product comprise studies with a quadruple vaccine containing pertussis and poliomyelitis vaccines as well (Ref. 1). The adjuvant effect of pertussis vaccine is such that these cannot be accepted as evidence for efficacy of this preparation. There are, however, good data that indicate that this preparation is efficacious when used for reinforcement of immunization in previously immunized children.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* During the 10 years, 1962 to 1972, a few million doses of this preparation were distributed; only three reactions, all local, were reported. However, administration of this preparation to institutionalized adults yielded high rates of severe reactions.

c. *Benefit/risk ratio.* The risk of untoward reactions to this preparation, when used as recommended in children, is negligible. Efficacy of this preparation when used for booster immunization to diphtheria and tetanus is satisfactory. When used for primary immunization, its efficacy is probably satisfactory but data are not available to permit a definitive conclusion.

4. *Critique.* This is a widely used adsorbed combined preparation of diphtheria and tetanus toxoids employed for the primary immunization of children and reinforcement of immunity to tetanus and diphtheria in children. Unfortunately conclusive data documenting efficacy as a primary immunizing agent are not available.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required. The manufacturer should specify the preferability of the trivalent preparation containing diphtheria and tetanus toxoids and pertussis vaccine, adsorbed, for the primary immunization of infants and children.

Diphtheria and Tetanus Toxoids Adsorbed Manufactured by Dow Chemical Company

1. *Description.* This product contains 14 to 17 Lf of diphtheria toxoid, 7 to 10 Lf of tetanus toxoid, and not more than 5 mg of potassium alum per dose in 0.3 N glycine, with 1:10,000 thimerosal. The toxoids are fractionated by the alcohol method.

2. *Labeling*—a. *Recommended use/indications.* Two intramuscular injections of 0.5 mL each 4 to 6 weeks apart, with a reinforcing dose of 0.5 mL about 1 year later, are recommended for immunization of infants and children under 6 years, when pertussis immunization is not indicated. In older children, its use is permissible if they are first screened by Schick or Moloney tests, but the adult type preparation is preferred. Booster doses are recommended following exposure to diphtheria. The labeling recommends three primary doses for immunization of infants (without explanation).

b. ***Contraindications.*** Detailed precautions concerning anaphylactoid reactions are outlined. Immunization should be deferred in the presence of acute infections or immunosuppressive treatment or the presence of a polio outbreak. Fractional doses of single antigens should be used in children with allergies, brain injury, or a history of severe reactions, etc. Various other precautions are included.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data on the specific product are presented.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data on this specific product are presented.

c. *Benefit/risk ratio.* In the absence of data, assessment of the effectiveness of this product for primary immunization is not possible. The benefit-to-risk assessment for this product when used for booster immunization is satisfactory.

4. *Critique.* This is a fairly typical combination of diphtheria and tetanus toxoids for pediatric use. The toxoids are fractionated by a well-established method, but the alum content appears somewhat low. The contraindications given are surprisingly detailed and the recommendations for three primary injections in infants are not explained. The data presented on efficacy and safety are derived from published papers on other products, but not on this specific product.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Diphtheria and Tetanus Toxoids Manufactured by Eli Lilly and Company

1. *Description.* This is an alcohol fractionated toxoid (Pillemer method) and contains 7.5 Lf tetanus toxoid and 25 Lf diphtheria toxoid per 0.5 mL dose. It is preserved with 1:10,000 thimerosal and is diluted in 0.3 molar glycine solution.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for active immunization of children under 6 against diphtheria and/or tetanus in circumstances where use of DTP may be contraindicated. The package circular recommends that three 0.5 mL doses by given subcutaneously at intervals of 4 to 6 weeks for primary immunization and that a reinforcing dose of 0.5 mL be given to children under 6 years of age about 1 year after the primary series. A booster dose is recommended at the time of entry into school (about 5 years of age).

b. *Contraindications.* These include active infections, possible exposure to polio, a history of central nervous system damage, or convulsions.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data on primary or secondary responses to this specific product were provided.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data from detailed studies on this specific product were provided. Data from the manufacturer's complaint files indicated only a low rate of consumer complaints concerning reactions, all of which were mild.

c. *Benefit/risk ratio.* If the product is demonstrated to have satisfactory immunogenicity in the age group for which recommended, the benefit-to-risk assessment would be satisfactory for primary immunization, and is satisfactory for booster immunization.

d. *Labeling.* The labeling is slightly inconsistent with the current recommendations of the Public Health Service Advisory Committee on Immunization Practices and the American Academy of Pediatrics in that the latter groups recommend that Td be used for children over 6. Accordingly, the labeling should be modified to recommend that the product be used for children "six and under" (rather than "for children under six").

The labeling should also be modified to reflect the well-documented advantages of the adsorbed product over the fluid product.

4. *Critique.* This submission is lacking in human data to demonstrate the ability of this product to elicit satisfactory primary or booster antitoxin responses in children of the age group concerned. In conjunction with a study of this type, detailed observations on reactogenicity should also be made.

In addition, the continued need for the fluid product is indeed questionable in view of the superiority of adsorbed toxoids as immunizing agents. Nonetheless, some physicians prefer the fluid product.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Diphtheria and Tetanus Toxoids Adsorbed Manufactured by Eli Lilly and Company

1. *Description.* This is an alcohol fractionated toxoid (Pillemer method) and contains 7.5 Lf tetanus toxoid and 25 Lf diphtheria toxoid per 0.5 mL dose. The adsorbed (alum precipitated) product is stated to contain 7.25 mg or less of alum per mL. It is preserved with 1:10,000 thimerosal and is diluted in 0.3 molar glycine solution.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for active immunization of children under 6 against diphtheria and/or tetanus in circumstances where use of DTP may be contraindicated. The package circular recommends that two 0.5 mL doses be given intramuscularly at an interval of 4 to 6 weeks for primary immunization and that a reinforcing dose of 0.5 mL be given 1 year later. A booster dose of 0.5 mL is recommended at the time of entry into school (about 5 years of age).

b. *Contraindications.* These include active infections, possible exposure to polio, a history of central nervous system damage, or convulsions.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data on primary or secondary responses to this specific product were provided.

b. *Safety—Animals.* This product meets Federal requirements.

(2) *Human.* No data from detailed studies on this specific product are provided. Data from the manufacturer's complaint files indicated only a low rate of consumer complaints concerning reactions, all of which were mild.

c. *Benefit/risk ratio.* If the product is demonstrated to have satisfactory immunogenicity in the age group for which recommended, the benefit-to-risk assessment would be satisfactory for primary immunization, and is satisfactory for booster immunization.

d. *Labeling.* The labeling is slightly inconsistent with the current recommendations of the Public Health Service Advisory Committee on Immunization Practices and the

American Academy of Pediatrics in that the latter groups recommend that Td be used for children over 6. Accordingly, the labeling should be modified to recommend that the product be used for children "six and under" (rather than "for children under six").

The labeling should also be modified to reflect the well-documented advantages of the adsorbed product over the fluid product.

4. *Critique.* This submission is lacking in human data to demonstrate the ability of this product to elicit satisfactory primary or booster antitoxin responses in children for the age group concerned. In conjunction with a study of this type, detailed observations on reactogenicity should also be made.

In addition, the continued need for the fluid product is indeed questionable in view of the superiority of adsorbed toxoids as immunizing agents. Nonetheless, some physicians prefer the fluid product.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Diphtheria and Tetanus Toxoids Adsorbed Manufactured by Lederle Laboratories Division, American Cyanamid Co.

1. *Description.* This product is a combined diphtheria and tetanus toxoid contained in physiological saline, 0.85 percent, with 0.01 percent thimerosol added as preservative. Formaldehyde is used as the toxoiding agent with both toxins, which are then purified by the Pillemer Alcohol Fractionation Method, diluted with phosphate buffer, with aluminum phosphate being added to a final concentration of 2.0 mg per mL. Each 0.5 mL dose contains 12.5 Lf of diphtheria toxoid and 5 Lf of tetanus toxoid, in addition to 1 mg of aluminum phosphate.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for use as a primary immunizing agent against tetanus and diphtheria in infants and children less than 6 years of age. The package insert does not clarify the differences between this product and DPT, nor the difference between this product and the adult Td preparation.

b. *Contraindications.* Acute respiratory disease or other active infection is suggested as a reason to defer immunization.

3. *Analysis*—a. *Efficacy—(1) Animal.* This product meets Federal requirements.

(2) *Human.* The general body of data supporting the human efficacy of diphtheria and tetanus toxoids is cited (Ref. 2), but no information is provided relative to the use of this specific product as produced by Lederle Laboratories.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No controlled data are presented on the safety of this product in humans. The submission notes that many hundred thousands of doses were distributed through the years 1970 to 1972, whereas during the period 1969 through June 1973, seven complaints were received by the manufacturer. These included local reactions, redness, and induration at the site of injection.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product cannot be satisfactorily assessed, owing to the lack of data in support of the efficacy of this product when used for primary immunization in humans. The benefit-to-risk assessment of this product when used for booster immunization is satisfactory.

4. *Critique.* The major defect in this submission is the absence of data to support the immunogenicity of this product when used for primary immunization in infants and children 6 years of age and under.

The labeling strongly suggests that a primary immunizing series is 2 intramuscular doses of 0.5 mL each. The "reinforcing dose" recommended 1 year after completion of the primary immunization is, in fact, part of the primary immunizing series. The labeling should clarify this point, and emphasize that immunization should not be considered complete until the third dose has been given.

The labeling fails to clarify when this preparation should be used in lieu of triple antigen (DPT) and fails further to establish the difference between the DT preparation for use in children 6 years of age and under and the adult Td preparations.

The advertising submitted by Lederle Laboratories was apparently last revised in December 1963, and differs strikingly from current recommendations.

5. *Recommendations.* The panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Diphtheria and Tetanus Toxoids Adsorbed Manufactured by Massachusetts Public Health Biologic Laboratories

1. *Description.* This product contains 15 Lf per mL diphtheria toxoid and 15 Lf per mL tetanus toxoid, adsorbed on 4.0 mg per mL aluminum phosphate, preserved with thimerosal in dilution 1:10,000 in a diluent of 0.01 M sodium acetate and 0.1 M sodium chloride, pH 6.0 ± 0.1. In the production of tetanus toxoid, the modified Mueller medium is used.

2. *Labeling*—a. *Recommended use/indications.* This preparation is recommended for primary or booster immunization against diphtheria and tetanus of children 6 years of age or less when immunizing preparations containing pertussis vaccine would be considered undesirable. Two intramuscular doses of 0.5 mL are given 4 to 6 weeks apart, followed by a reinforcing dose approximately 1 year later.

b. *Contraindications.* These include acute infectious illnesses.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* References to the literature of several animal studies are given in the manufacturer's data submission to the Panel (Ref. 3). This product meets Federal requirements.

(2) *Human.* Serologic studies have shown combination vaccines including the pertussis component to be efficacious. Likewise, diphtheria and tetanus toxoids have been shown to be efficacious in adults not only for booster purposes but also for primary immunizations. Studies of tetanus and diphtheria toxoids in children are lacking. However, since these toxoids have been shown effective for primary